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Original article

Persistent rhinitis – allergic or nonallergic?

Summary Although rhinitis has been classified as being either allergic, noninfectious, or "other forms" (nonallergic noninfectious), these categories lack strict classification criteria and often overlap. The term "nonallergic noninfectious rhinitis" is commonly applied to a diagnosis of any nasal condition, in which the symptoms are similar to those seen in allergic rhinitis but an allergic aetiology has been excluded. This group comprises several subgroups with ill-defined pathomechanisms, and includes idiopathic rhinitis, irritative-toxic (occupational) rhinitis, hormonal rhinitis, drug-induced rhinitis, and other forms (non-allergic rhinitis with eosinophilia syndrome [NARES], rhinitis due to physical and chemical factors, food-induced rhinitis, emotion-induced rhinitis, atrophic rhinitis). Unlike allergic rhinitis, there are no specific diagnostic tests and diagnosis is primarily based on a history of reaction to specific irritant-toxic triggering agents (either general or occupational), drugs, infections, and hormonal status, coupled with exclusion of allergic rhinitis and other forms of non-allergic rhinitis by skin prick testing. Accordingly, from a clinical standpoint NARES, irritative-toxic, hormonal, drug-induced and idiopathic rhinitis are possibly the least difficult forms of nonallergic rhinitis to diagnose.

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Key words: NANIPER; NARES; irritative-toxic rhinitis; hormonal rhinitis; post-infectious rhinitis; idiopathic rhinitis.

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Rhinitis is a disease that is often trivialized despite being the cause of widespread morbidity, increased medical treatment costs, reduced work productivity and lost school days, and not least due to the difficulty in definition and classification of the disease. Although diagnosis of rhinitis is generally made on the basis of two or more nasal symptoms, which include nasal congestion, rhinorrhea, sneezing/itching, and impairment of smell, for greater than one hour most days (1), it is more difficult to determine whether or not these symptoms are clinically persistent and/or relevant. It is well known for example, that cold dry air leads to manifestation of some of these symptoms, leading to a condition known as "skier's nose", which is temporal and not truly pathologic. Furthermore, 95% of normal subjects, without any rhinitis complaints, have recently been shown to sneeze up to 4 times a day and to blow their noses up to four times a day, as an average over 2 weeks (2). This suggests that five or more sneezes and/or nose blowings/day may possibly be indicative of clinically relevant nasal disease.

Once diagnosis of rhinitis has been made from a clinical viewpoint, the disease has to be classified from a number of possibilities. Although the international consensus report on the diagnosis and management of rhinitis (1) has classified rhinitis as being structural, infectious, allergic or "other forms", these categories are not entirely appropriate due to the lack of strict classification criteria, which are often confusing and overlapping. More recently, noninfectious rhinitis has generally been classified as being either allergic or nonallergic, depending predominantly on whether or not an allergic etiology is indicated.

However, unlike allergic rhinitis there are no specific diagnostic tests for nonallergic rhinitis, and diagnosis is primarily made on the basis of rhinitis symptoms in the absence of identifiable allergy (by allergy testing), structural abnormality, immune deviation, or sinus disease. Although inflammation has been demonstrated to be an integral component of allergic rhinitis, even in nonsymptomatic patients, there is great debate regarding this facet in nonallergic rhinitis, since some studies have suggested that exclusion of inflammation is indicative of nonallergic rhinitis and other studies have demonstrated that most of the nonallergic rhinitis patients have some degree of inflammation (3). Furthermore, it is evident that the incidence of positive skin tests to inhalant allergens is far greater than the incidence of rhinitis symptoms in large cross-sectional epidemiological studies, suggesting that both allergic and nonallergic rhinitis patients are capable of demonstrating skin test positivity (Fig. 1). This also implies that rhinitis symptoms in a patient with a positive skin test are not necessarily caused by the allergen and that the contribution of nonallergic rhinitis to the total number of rhinitis patients may be substantially greater than hitherto estimated. Indeed, a recent survey of nearly 1000 rhinitis patients seen in 18 allergy clinics in the USA demonstrated that 43% of the patients had pure allergic rhinitis, based on their symptoms and positive skin test and 23% had pure nonallergic rhinitis based on symptoms but negative skin tests. Furthermore, the survey

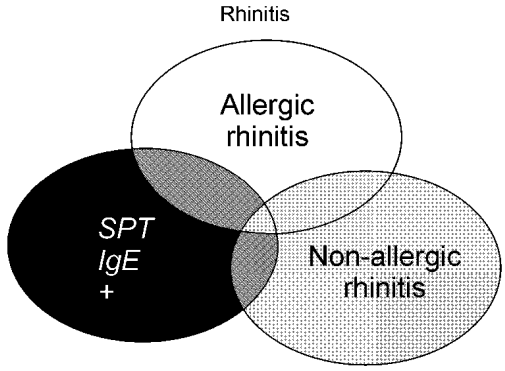

Figure 1. Schematic representation of allergic and nonallergic patients demonstrating skin test positivity.

demonstrated that 34% of the patients were diagnosed with "mixed" rhinitis (a combination of allergic and nonallergic rhinitis), based on a positive skin test but not complete accordance between the symptoms and skin test results (4), suggesting that it is important to consider not only the allergic and nonallergic, but also the mixed etiology of rhinitis in order to manage the disease in these individuals most effectively.

Although nonallergic rhinitis has not been as extensively investigated as allergic rhinitis and there is comparatively little information on the underlying mechanisms, it is nevertheless likely that nonallergic rhinitis may be just as common and disabling for the patient, as allergic rhinitis. Furthermore, studies of prevalence of nonallergic rhinitis have reported that this ranges from around 20–50% amongst the rhinitic population (5, 6).

Non-infectious nonallergic rhinitis

The term "noninfectious nonallergic rhinitis" is commonly applied to a diagnosis of any nasal condition in which the symptoms are identical to those seen in allergic rhinitis but an allergic etiology has been excluded. Whilst it is difficult to readily diagnose nonallergic rhinitis, it has been suggested that in patients with perennial nonallergic rhinitis, this condition persists for greater than 9 months each year and produces two or more symptoms, including hypersecretion, blockage, sneezing and postnasal drip. Currently, this is a diagnosis of exclusion, with no generally accepted definition or diagnostic criteria, and comprises several subgroups with ill-defined pathomechanisms. These nonallergic etiologic entities can broadly be classified as: (i) idiopathic rhinitis (also referred to as vasomotor rhinitis, or nonallergic noninfectious perennial rhinitis, NANIPER); (ii) irritative-toxic (occupational) rhinitis; (iii) hormonal rhinitis; (iv) drug-induced rhinitis; and (v) other forms (nonallergic rhinitis with eosinophilia syndrome [NARES], rhinitis due to physical and chemical factors, food-induced rhinitis, emotion-induced rhinitis, atrophic rhinitis) (7, 8). From a clinical standpoint NARES, irritative-toxic, hormonal, drug-induced and idiopathic rhinitis are possibly the least difficult forms of nonallergic rhinitis that can be diagnosed, and will therefore be discussed further.

Types of nonallergic rhinitis

Non-allergic rhinitis with eosinophilia syndrome (NARES)

The condition "nonallergic rhinitis with eosinophilia syndrome" (NARES) was originally characterized on the basis of the presence of greater than 20% eosinophils in nasal smears of symptomatic patients with perennial sneezing attacks, a profuse watery rhinorrhea, nasal pruritis, nasal obstruction and occasional loss of smell (5, 9, 10). In addition to these symptoms, a marked feature of the disease was the lack of evidence of allergy, as indicated by negative skin prick tests and/or absence of serum IgE antibodies to specific allergens.

The prevalence of NARES has been shown to range between 13 and 33% in patients with nonallergic rhinitis (11, 12). Although the specific etiology of NARES is not clear, in view of the features shared by this syndrome and the ASA triad (nasal polyposis, intrinsic asthma, and intolerance to aspirin) and because NARES patients frequently develop nasal polyps and asthma later on in life, it has been suggested that NARES may be an early expression of the triad (12). Indeed, in about 50% of NARES patients without a history of respiratory symptoms, bronchial responsiveness is associated with an increase in the number of sputum eosinophils, but not with an increase in the number of nasal eosinophils (13). Some investigators have suggested that NARES is a variant of vasomotor rhinitis, and referred to the condition as "perennial intrinsic rhinitis" (14).

Irritative-toxic (occupational) rhinitis

Irritative-toxic rhinitis, as the term implies, may be defined as rhinitis caused by exposure to airborne irritant or toxic agents such as chemicals, glues, solvents, cigarette smoke and small molecules in the work place. These agents act via nonimmunologic mechanisms, and elicit irritation, nasal obstruction, watery secretion, postnasal drip and sneezing (7, 10, 15). Whilst the specific mechanisms underlying the effects of these irritants and toxic agents have not been fully elucidated, it is possible that damage and/or stimulation of nasal epithelial cells and neurons by the irritants may lead to synthesis of pro-inflammatory mediators and neuromediators. These mediators predispose the nasal mucosa to inflammation and infection, and subsequently result in the symptoms of rhinitis. Indeed, studies of the effects of exposure to airborne nonallergenic microbial agents e.g. endotoxin and beta(1,3)-glucan) in compost workers (16), and vanadium pentoxide, a respiratory irritant constituent of fuel oil ash, in boilermakers (17), have demonstrated

that these agents lead to pro-inflammatory changes in the nasal mucosa of these workers.

This form of rhinitis, however, is often associated with sinus, bronchial and conjunctival effects, and in about 70% of the patients these symptoms are decreased when the triggering agent/s are avoided, for example when the patient is away from work on holidays, and during weekends.

Hormonal rhinitis

Hormonal rhinitis is often associated with hypothyroidism, acromegaly, and pregnancy, in particular, although it has also been noted in postmenopausal women and older men (7, 10). A large multicenter study has recently indicated that the cumulative incidence of pregnancy rhinitis was 22%, and in women who were smokers this was significantly increased with a relative risk enhancement of 69% (18). Compared with pregnancy rhinitis, the evidence linking hypothyroidism with nasal pathology is sparse, and the reported increase in nasal secretion associated with thyroid disease is anecdotal (7). However, as is the case for irritative-toxic rhinitis, there is no evidence of an underlying immunologic mechanism, and patients complain of nasal obstruction, watery secretion, postnasal drip, sneezing and irritation (7, 10).

Although the precise mechanisms underlying hormonal rhinitis are not clear, some studies of sex hormones have suggested that these may influence nasal inflammation. Whilst estrogens normally lead to vascular engorgement in the female genital tract, these have also been shown to have a similar effect in the nose, which leads to nasal obstruction and/or nasal hypersecretion. Beta-estradiol and progesterone have been shown to increase the expression of histamine H_1 receptors on human nasal epithelial cells and mucosal microvascular endothelial cells (19), and to induce eosinophil migration and/or degranulation (20). These effects are in marked contrast to those of testosterone, which decreases eosinophil activation and viability (20).

Drug-induced rhinitis

Several commonly employed medications, such as aspirin, other nonsteroidal anti-inflammatory drugs (NSAIDs), beta-blockers, angiotensin-converting enzyme (ACE) inhibitors, methyldopa, oral contraceptives, psychotropic agents, and nasal topical decongestants (oxymetazoline, naphazoline, xylometazoline) may induce symptoms of rhinitis when they are administered either topically or systemically. Drug-induced rhinitis may be subdivided into either a predictable "pharmacologic", or an unpredictable "aspirin hypersensitivity" type.

Whether an individual develops intolerance to aspirin and/or NSAIDs is unpredictable, and predominantly produces rhinorrhea, which may be either isolated or part of a complex involving hyperplastic rhinosinusitis, nasal polyps and asthma (7). Although there are currently no specific tests for the diagnosis of aspirin-induced rhinitis, it has been suggested that patients suffering from aspirin hypersensitivity may have increased numbers of eosinophils in both the nasal secretions and blood, which respond to topical steroid treatment. It is also possible that oral or nasal aspirin challenge may be useful to diagnose this condition, as has been shown to be the case for aspirin-induced asthma, although not all patients with a history of aspirin sensitivity react to aspirin provocation (21).

In contrast, nasal reactions to systemic drugs such as reserpine, guanethidine, methyldopa, ACE-inhibitors, α-antagonists, β-blockers, etc., are infrequent, but predictable side-effects of specific drugs, and often documented on drug information leaflets for patients. These agents lead to predominantly nasal blockage, although watery secretion, postnasal drip and sneezing are accompanying symptoms (7). Persistent over-use of the topical nasal vasoconstrictors also leads to nasal decongestion by a mechanism involving a rebound effect following withdrawal of these drugs, and excessive use of these agents may result in nasal hyperreactivity and hypertrophy of the nasal mucosa, leading to a condition known as "rhinitis medicamentosa" (7, 10).

Post-infectious rhinitis

This condition normally prevails following a persistent viral or bacterial infection, and is characterized by nasal obstruction, watery secretion, postnasal drip, and sneezing. The symptoms are frequently self-limiting and respond to treatment with topical steroids. However, when the symptoms are persistent and similar to those noted for chronic sinusitis, this condition should be dissociated from chronic sinusitis by appropriate diagnostic means such as CT scan.

Idiopathic rhinitis

Idiopathic rhinitis (sometimes also referred to as vasomotor rhinitis; noninfectious nonallergic rhinitis [NINAR]; or nonallergic noninfectious perennial rhinitis [NANIPER]) is characterized primarily by symptoms of nasal blockage, rhinorrhea and sneezing, although the prevalence of sneezing, conjunctival symptoms and pruritis is lower than that in allergic rhinitis. Although the subjects have traditionally been classified as either "runners" (those with predominantly rhinorrhea) or "blockers" (those with predominantly nasal congestion and blockage), many patients suffer from more than one type of these symptoms, therefore making it difficult to subdivide the patients into these groups. The etiology is unknown in most cases and the disease may possibly be triggered by irritants and changes in atmospheric conditions (22). Although attempts to differentiate idiopathic rhinitis patients from normal subjects have generally been based on nasal hyperreactivity to histamine, methacholine, or capsaicin, some studies have demonstrated that cold dry air (CDA) challenge may

allow a better differentiation of idiopathic rhinitis patients from normal subjects (23). However, none of these tests is suitable to differentiate nonallergic idiopathic rhinitis from other forms of rhinitis, nor has any been demonstrated to be superior to a simple case history.

Some mechanistic studies have suggested that the functional abnormality of the nasal mucosa may be associated with sensory afferent nerve and/or C-fiber stimulation, since nasal provocation with capsaicin results in a dose-dependent leukocyte influx, albumin leakage and glandular secretion in patients with allergic rhinitis (24). However, reports on the underlying mechanisms are conflicting since there is little evidence of eosinophilia or local inflammation in idiopathic rhinitis patients. A recent study comparing the effects of forced expiration through the nose in idiopathic patients and nonrhinitic controls demonstrated that there was a significant increase in nasal airway resistance, but not mucous production or sneezing, in idiopathic rhinitis patients but not controls. This suggests that also mechanical stimulation may be a possible mechanism in idiopathic rhinitis patients compared with controls (25) (Fig. 2).

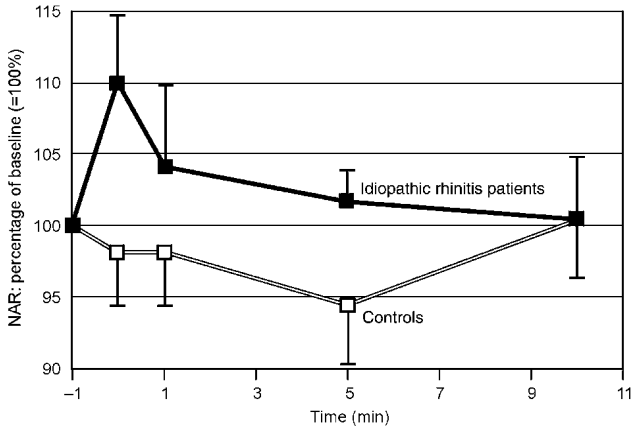

Figure 2. Effect of peak nasal expiratory flow rate (forced nasal expiration) on nasal airway resistance (NAR) in idiopathic rhinitis patients and controls. (Modified from Braat et al. 2000 (25) and reprinted with kind permission.)

Conclusion

Although there is a general difference in opinion amongst clinicians and researchers regarding the classification of different forms of nonallergic rhinitis, it may be possible to group some of these conditions together from a clinical standpoint. This is particularly so in view of the limited information available on the underlying mechanisms and possibly the comparatively lesser difficulty in diagnosis of these conditions. Whilst no specific diagnostic test is available for many of these forms of nonallergic rhinitis, a clinical diagnosis is primarily based on a history of reaction to specific irritant-toxic triggering agents (either general or occupational), drugs, infections, and hormonal status, coupled with exclusion of allergic rhinitis and other forms of nonallergic rhinitis by skin prick testing. Assessment of nasal and blood eosinophilia, in particular is also important. Recent evidence suggests that relevant diagnostic tools and specific information regarding the mechanisms underlying some of these conditions is more forthcoming and should therefore lead to a better overall understanding and management of these conditions in the future.

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General discussion

Ciprandi: Is there a relationship between nonallergic rhinitis and asthma, or nonallergic rhinitis and conjunctivitis?
Bachert: In daily clinical practice we do not see a relationship of nonallergic rhinitis with conjunctivitis, but it has been demonstrated that the risk to suffering from asthma is increased in patients with nonallergic rhinitis compared with normal subjects. If you think from the opposite angle looking at patients with lower airway diseases such as asthma or COPD, many of these individuals may also show disease in the upper airways, which partially may not have an immunologic etiology. We do know that in smokers with or without bronchial symptoms, there are changes in the nasal mucosa and these patients have nasal complaints, such as dry crusty nose.
Delegate: How would you find inflammation in nonallergic patients and how would you discern between this inflammation and that present under normal conditions? That is, how could I be certain that this inflammation in the nose was genuinely disease associated?
Bachert: Actually in daily practice you can measure the number of eosinophils, which should be greater than 20%. However, a major problem with this is that we do not have a standardized technique and baseline value. We have been trying to standardize this approach and have found that it depends on the sampling technique used for nasal eosinophils. We have used nasal washings and nasal brushings and found that we get completely different results with each technique. Another alternative may be to measure mediators such as ECP, which would possibly give a better indication of exacerbated inflammation and normal baseline inflammation. However, this is not daily clinical practice yet, which rather is based on the history of the patient, and appropriate treatment.
Garay: If neurogenic inflammation is involved, then it may be possible to measure substance P to confirm this.
Bachert: Also I am not aware of any study that indicates a cut-off value for this mediator, which would help in diagnosis.
Delegate: For the study, in which you described patients with mixed rhinitis, is nasal hyperreactivity in these patients really a nonallergic component of allergic inflammation?
Bachert: You can find nasal hyperreactivity in patients with both allergic and nonallergic rhinitis. For example, it is possible to differentiate a population of allergic rhinitis patients from a population of nonallergic normal patients by doing dose-ranging nasal provocation with histamine. However, in the study I mentioned in patients with mixed rhinitis, their disease was classified on the basis of distribution of symptoms throughout the year. Hence, these patients could be positive in skin prick testing to a specific seasonal allergen, but they had symptoms throughout the year.
Delegate: Should we also measure nasal hyperreactivity as a way to differentiate between allergic and nonallergic rhinitis?
Bachert: Nasal hyperreactivity is present in both allergic and nonallergic rhinitis, and it does not discriminate between these conditions.